REMARKS

Claim Status

Claims 1-26 and 28-36 are pending in the present application.

Claim 1 is amended to characterize a select embodiment. Support may be found on page 6, line 6 and page 7, line 2 of the specification.

Claims 2 and 23 are cancelled without prejudice.

Claims 24 and 25 are amended to maintain antecedent basis.

Claim 26 is amended to characterize a select embodiment. Support may be found on page 6, line 6 and page 7, line 2 of the specification.

These changes do not involve any introduction of new matter. Consequently, entry of these changes is respectfully requested. No additional claims fee is believed to be due.

Response to Double Patenting Rejection

Claims 1-5, 23, 26, 31, 35, and 36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 11, 12, and 20 of copending Application No. 10/841,193. Since the rejection is provisional as being based upon an application, Applicant requests that the rejection be held in abeyance until such time that Application No. 10/841,193 is allowed and issues as a patent.

Claims 1-5, 21-24, 31, 32, 35, and 36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5-13, and 18 of copending Application No. 10/977,848. Since the rejection is provisional as being based upon an application, Applicant requests that the rejection be held in abeyance until such time that Application No. 10/977,848 is allowed and issues as a patent.

Claims 1-3 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 4-16 of copending Application No. 10/152,924. Since the rejection is provisional as being based upon an application, Applicant requests that the rejection be held in abeyance until such time that Application No. 10/152,924 is allowed and issues as a patent. The Office states, "Applicants submit that they would file a terminal disclaimer upon notice of allowable subject matter." Applicant has made no statement to this effect. Applicant asserts that discussion of a terminal disclaimer is premature until the rejection is made "non-provisional."

Rejection Under 35 U.S.C. §103(a)

Claims 1-5, 21, 23-24, 26 and 28-29 are rejected under 35 USC § 103(a) over U.S. Patent No. 6,284,802 to Bissett et al. ("Bissett"). In support for the rejection, the Office states:

> Bissett et al. discloses the use of vitamin B3 compounds in skin care compositions. (Column 33, claim 3). Example 1 discloses a composition with 2% niacinamide, a vitamin B3 compound. (Column 30, lines 1-5; Column 16-17, section titled "Vitamin B3 compounds"). Water, glycerin and silicone fluids are disclosed in emulsions and are considered carriers. (Example 2). Hexamidine is disclosed as useful as an antimicrobial adduct. (Column 23, line 45-55).

The Office concedes that "Bissett does not exemplify a composition comprising hexamidine." The Office concludes that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a skin care composition comprising hexamidine, and vitamin B3 and additional ingredients such as peptides, additives claimed in claim 3, and tocopherol acetate since all ingredients are well known for their use in skin care preparations and useful for compositions for skin care as disclosed in Bissett et. al." Applicant traverses the rejection on several grounds. Applicant continues to assert that the combination of hexamidine and vitamin B_3 yields unexpected and unappreciated results related to the regulation of mammalian keratinous tissue. A declaration was previously submitted under 37 C.F.R. §1.132 from Rosemarie Osborne, Ph.D., in support of the assertion of unexpected results.

First, the Office has failed to give proper weight and consideration to the declaration. The Office argues that "the results presented in the declaration merely concern the activation of various genes in *in vitro* culture and the speculation that these genes may produce a beneficial effect *in vivo* for the combined composition when administered to the skin. Absent the demonstration of actual therapeutic effect, this example is not persuasive to demonstrate actual unexpected results for the claimed compositions." The Office is directed to paragraph 3 of the declaration. Dr. Osborne states, "These types of skin cultures are accepted as surrogates for natural human skin for transplantation in burn and skin ulcer patients[1,2,3,4] and for *in vitro* testing to assess the effects of chemicals and products[5,6,7,8], including tests that are international

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[1] Bello YM, Falabella AF, Eaglstein WH. Tissue-engineered skin. Current status in wound healing. *Am J Clin Dermatol* 2001 2(5):305-13.

[2] Horch RE, Kopp J, Kneser U, Beier J, Bach AD. Tissue engineering of cultured skin substitutes. *J Cell Mol Med* 2005 Jul-Sep;9(3):592-608.

[3] Shakespeare PG. The role of skin substitutes in the treatment of burn injuries. *Clin Dermatol.* 2005 Jul-Aug 23(4):413-8.

[4] Supp DM, Boyce ST. Engineered skin substitutes: practices and potentials. *Clin Dermatol.* 2005 Jul-Aug 23(4):403-12.

[5] Osborne R, Perkins MA. An approach for development of alternative test methods based on mechanisms of skin irritation. *Food Chem Toxicol* 1994 Feb 32(2):133-42.

[6] Fentem JH, Botham PA. ECVAM's activities in validating alternative tests for skin corrosion and irritation. *Altern Lab Anim* 2002 Dec 30 Suppl 2:61-7.

[7] Ponec M. Skin constructs for replacement of skin tissues for in vitro testing. *Adv Drug Deliv Rev* 2002 Nov 1 54 Suppl 1:S19-30.

government regulatory agency standards[9]." As evidenced by Dr. Osborne's declaration and the references cited, skin cultures are accepted as surrogates for natural human skin. The Office provides no technical reasoning for why skin cultures should not be accepted as surrogates for natural human skin. The Office appears to be relying on its unsubstantiated understanding of the state of the art in lieu of the declarant's understanding of the state of the art. Applicant asserts that the declaration from one skilled in the art has not been sufficiently considered by the Office.

Second, the Office argues that "the instant claims claim an extremely broad range of concentrations of the active ingredients, from about 0.0001% to about 25%. The experiments undertaken in the declaration are not sufficient to demonstrate a synergistic effect over such as broad range of concentrations and in every ratio that is included within the broad scope of the claims." In efforts to advance prosecution, Applicant has amended the claims such that the Office's assertion of the claims covering "an extremely broad range of concentrations" is believed to be moot. However, Applicant wishes to address comments made by the Office. Specifically, the Office states, "According to MPEP 716.02(d), Whether (sic) the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results **must** be reviewed to see if the results occur over the entire claimed range" (emphasis added). Case law does not support the breadth to which the Office gives this passage.

In the case of *In re Clemens*, 622 F.2d 1029,1036, 206 USPQ 289,296 (CCPA 1980) which is cited by MPEP § 716.02(d), the court notes that nonobviousness can be established by a narrow range of data if the data can be reasonably extended to prove the broader claimed range. Applicant presents this case law to refute the Office's assertion that unexpected results must be shown over an entire claimed range. However, as stated previously, in efforts to advance prosecution, Applicant has amended the claimed range thereby addressing the Office's concern.

In light of the discussion presented above, Applicant asserts that the claimed invention is patentably distinct over the cited reference. The declaration evidences the unexpected results from the combination of hexamidine and a vitamin B_3 compound. The data provided demonstrates a statistically significant and substantial synergistic effect.

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[8] Welss T, Basketter DA, Schroder KR. In vitro skin irritation: facts and future. State of the art review of mechanisms and models. *Toxicol In Vitro* 2004 Jun 18(3):231-43.

[9] OECD, 2004. OECD guideline for testing of chemicals, No. 431: In Vitro Skin Corrosion: Human Skin Model Test. Organisation for Economic Co-operation and Development, Paris, France.

Applicant further asserts that the declaration demonstrates the patentability of the claimed invention as understood from the directives of the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 82 U.S.P.Q.2D 1385 (2007). Throughout its decision, the Supreme Court emphasized the importance of "predictability" in the determination of obviousness. For example, the Supreme Court stated:

- "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable result."
- "The Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result."
- "[A] court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions."

These passages illustrate a common theme in the Supreme Court's analysis of obviousness. The determination of obviousness relates to predictability. The declaration provided by Applicant evidences the unpredictability of the combination of hexamidine and vitamin B3 - namely, through the synergistic regulation of genes that are fundamental to processes for regulating the condition of mammalian keratinous tissues such as skin. Applicant asserts that this unpredictability alone is a sufficient basis for a conclusion of nonobviousness and allowance of the claims as patentably distinct over the cited references.

Applicant request reconsideration of the declaration in light of the discussion presented above. Withdrawal of the rejection and allowance of the claims is respectfully requested.

Claim 25 is rejected under 35 USC § 103(a) over Bissett further in view of U.S. Patent Publication No. 2003/0176366A1 to Castiel et al. ("Castiel"). The Office relies on Castiel to teach a composition comprising ascorbyl glucoside. The Office concludes that the combination of Bissett and Castiel would have been obvious to one of ordinary skill in the art at the time the invention was made. Castiel does not address the combination of hexamidine and the vitamin B3 compound and, therefore, does not resolve the deficiencies presented above in regard to Claim 1 (from which Claim 25 depends).

Claims 1-5, 23, 24, 26-29, 31, and 36 are rejected under 35 USC §103(a) over U.S. Patent No. 6,589,514 (hereinafter "Jensen") in view of Flick et al. ("Flick")(Cosmetic Additives – An Industrial Guide, Pages 647-648, 652; PTO-892) further in view of Gensler et al.

("Gensler")(Nutrition and Cancer, 29(2), 157-162; PTO-892), and JP2002212053 to Oblong et al. ("Oblong"). In support of this rejection, the Office presents Jensen as disclosing "compositions comprising hexamidine (0-1%), and carriers including water, seed oil and vegetable oil." The Office further states, "Jensen et al. discloses the use of panthenol in a skin care composition. Example two of Jensen . . . is a dematological composition including Morifina citrifola fruit juice, the retinoid retinyl palmitate and BHT." The Office concedes, "Jensen et. al. does not expressly disclose a composition comprising vitamin B3 or panthenol in combination with a hexamidine compound and a carrier."

The Office relies on Flick as disclosing "that panthenol is used in skin care products as a quick deep penetrating moisturizer, that aids in tissue repair and promotes normal keratinization." The Office states, "Flick et. al. further discloses commercial sources of various forms of vitamin E including a-tocopherol acetate." The Office concludes, "[P]anthenol and a-tocopherol acetate are considered as ingredients well known by on of ordinary skill in the arts in the cosmetic, pharmaceutical and skin care industry."

Next, the Office relies on Gensler as disclosing "that topical nicotinamide (also known by the chemical name niacinamide) presents the systemic immunosuppression and skin tumorigenesis . . .[and] prevention of phtocarcinogenesis (sic)." The Office concludes, "One or ordinary skill in the art would recognize protecting against UVB as a beneficial in a skin care composition."

Finally, the Office relies on Oblong as disclosing that "vitamin B3 compounds can have beneficial effects such as improving tactile discontinuities of the skin." The Office concludes:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a skin care composition comprising hexamidine, vitamin B3, panthenol, a-tocopherol acetate and a carrier because Jensen et. al. discloses skin care compositions comprising a-tocopherol acetate, hexamidine and discloses panthenol in skin care compositions and Flick et. al. discloses panthenol and a-tocopherol acetate as commercially available cosmetic additives and Gensler et. al. discloses that topical application of niacinamide and a-tocopherol can contribute to protection against UVB rays and Oblong et. al. discloses the beneficial effects of niacinamide such as regulating visible and tactile discontinuities of the skin. All the claimed steps herein are known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. All ingredients in the instant composition are well known in the prior art for use in skin care compositions with various beneficial effects. The combination of said ingredients results in a topical combination with expected results. Therefore, one of ordinary skill in the art would have reasonably expected that the use of hexamidine, vitamin B3, panthenol, and a-tocopherol in skin care

> compositions would have had beneficial effects such as moisturizing, maintenance of keratinization, protection against wrinkles and protection from UVB rays.

Applicant traverses the rejection on two grounds. First, a *prima facie* case of obviousness has not been established. Second, even if a *prima facie* case was established, the obviousness argument is overcome by the showing of unexpected results. Therefore, the claimed invention is unobvious and that the rejection should be withdrawn.

With regard to Claim 1, the references of interest are Jensen, Gensler, and Oblong. The Office argues that Jensen teaches a skin care compositions comprising α-tocopherol acetate, hexamidine and discloses panthenol and that Gensler and Oblong teach the use of niacinamide. Initially, Applicant contests the Office's application of Gensler. The Office states, "Gensler et. al. discloses that topical application of niacinamide and a-tocopherol can contribute to protection against UVB rays." Gensler states, "[W]e have demonstrated that topical nicotinamide prevents the systemic immunosuppresion and skin tumorigenesis induced by UVB irradiation. . . . Together with previous data showing inhibition of photoimmunosupression and photocarcinogenesis by α-tocopherol . . . the current results suggest that photoimmunosuppression is a valid target for skin cancer prevention." However, the composition used by Gensler is vastly different from the one claimed by the Applicant or proposed by the Office via Jensen.

Gensler discloses applying a solution of acetone and nicotinamide to mice. *See* pg. 157, 2nd col., last paragraph. Applicant asserts that a skilled artisan will readily recognize that acetone is not "a dermatologically acceptable carrier" as is required by Claim 1. The Office may argue that a skilled artisan could incorporate nicotinamide as taught by Gensler into the composition as taught by Jensen. However, case law suggests and the MPEP states, "A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art." See MPEP § 2143.02 (emphasis added); see also *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 1739 (2008)("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). With the present combination, the Office has failed to present whether the proposed combination would change the respective functions of the references. Specifically, Applicant asserts that the Office has failed to establish

a reasonable expectation of success that the proposed combination of nicotinamide in the composition of Jensen will prevent the systemic immunosuppresion and skin tumorigenesis induced by UVB irradiation as presented in Gensler. The Office presents no rationale for whether nicotinamide will exhibit the same effects as disclosed in Gensler when present in a carrier comprising *Morinda citrifolia* fruit juice, purified water, cyclomethicone, hydrogenated polyisobutene, cetyl alcohol, glycerin, *Morinda citrifolia* seed oil, glyceryl stearate, myristyl myristate, octyl palmitate, PEG-40 stearate, vegetable oil, and the other optional ingredients such as presented in Example 2 of Jensen. In other words, it is incumbent upon the Office to provide a reasonable expectation that the proposed combination will prevent skin tumorigenesis (*i.e.*, prevent development of skin tumors).

Having disposed of Gensler, the rejection of Claim 1 appears to be based upon the combination of Jensen and Oblong (as the Office's use of Flick is directed to teaching panthenol compounds and vitamin E). Applicant asserts that a *prima facie* case of obviousness has not been established. The Supreme Court state, "Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (U.S. 2007) quoting *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006). The Office has failed to provide reasoning or rationale to support the conclusion of obviousness. The Office argues that Jensen discloses skin care compositions comprising hexamidine and Oblong discloses the beneficial effects of niacinamide, yet provides no explanation of why Jensen should be combined with Oblong. Specifically, Jensen lists hexamidine as an optional ingredient in Example 2 (along with 14 other optional ingredients). However, Jensen provides no teaching or suggestion as to why hexamidine should be present in the composition of Jensen, and the Office provides no rationale for why hexamidine should be present in the proposed combination of Jensen and Oblong. The rejection appears to be based on the mere listing of hexamidine as an optional ingredient without the "articulated reasoning with some rational underpinning" as necessitated by the Supreme Court.

Even if a *prima facie* case was established, the obviousness argument is overcome by the showing of unexpected results and the unpredictability of the combination. The discussion of unexpected results is presented above (in regard to the rejection based on Bissett) and is applicable to the present rejection. Therefore, the claimed invention is unobvious and the rejection should be withdrawn.

Claim 26 – Claim 26 comprises elements (a) and (b) from Claim 1 and further includes the limitation of a panthenol compound. The Office states that Jensen discloses the use of panthenol in a skin care composition. The Office further relies on Flick for teaching the role of panthenol in skin care products. However, Flick does not address the combination of hexamidine and the vitamin B3 compound. Therefore, the arguments presented above with regard to Claim 1 are applicable to Claim 26.

Claims 2-5, 23, 24, 27-29, 31, and 36 – These claims depend from and contain all the limitations of either Claim 1 or Claim 26. Since Claims 1 and 26 are nonobvious in light of the arguments presented above, the claims dependent therefrom are also nonobvious.

Claims 21-24 are rejected under 35 USC §103(a) over Jensen in view of Gensler, Oblong, and PCT Publication WO 00/67722 to Mammone In support of the rejection, the Office states, "Mammone et al. discloses the use of N-acetyl glucosamine in skin care composition used for exfoliation and moisturization." The Office concludes that the combination of Jensen, Gensler, Oblong, and Mammone would have been obvious to one of ordinary skill in the art at the time the invention was made. Mammone does not address the combination of hexamidine and the vitamin B3 compound and,, therefore, does not resolve the deficiencies presented above in regard to Claim 1 (from which Claims 21-24 depend).

Claim 25 is rejected under 35 USC §103(a) over Jensen in view of Castiel and Oblong. In support of this rejection, the Office asserts:

> The instant application is a CIP of 10/379,252, filed 03/04/2003. However, the '252 application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for the instant new claim 25 of this application for CIP since the '252 application do not disclose the particular composition comprising ascorbyl glucoside recited in claim 25. Therefore, the filing date of claim 25 is deemed to be the filing date of the instant application, 02/17/2004.

The '252 application provides sufficient disclosure of a composition comprising ascorbyl glucoside. Claim 1 of the '252 application recites a skin care composition comprising a hexamidine compound, a safe and effective amount of a skin care active including vitamin B3, and an acceptable carrier. Claim 3, which is dependent from Claim 1, adds the element of an additional skin care active including skin lightening agents. On page 32, line 6 of the '252 application, ascorbyl glucoside is recited as a suitable skin lightening agent. Applicant asserts

that sufficient disclosure is present in the '252 application to justify a filing date of March 4, 2003 for Claim 25. Therefore, Castiel does not qualify as a 102(a) reference.

The Office relies on Castiel to teach a composition comprising ascorbyl glucoside. The Office concludes that the combination of Jensen, Oblong, and Castiel would have been obvious to one of ordinary skill in the art at the time the invention was made. Castiel does not address the combination of hexamidine and the vitamin B3 compound and, therefore, does not resolve the deficiencies presented above in regard to Claim 1 (from which Claim 25 depends).

CONCLUSION

This response represents an earnest effort to place the present application in proper form and to distinguish the invention as claimed from the applied reference(s). In view of the foregoing, it is requested that the Examiner reconsider and withdraw the rejections. Early and favorable action in the case is respectfully requested. Again, the Office is encouraged to contact the Applicant's representative should questions arise.

Respectfully submitted,

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